INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Research Paper

Comparative Analysis of Regulatory Requirements and Approval Pathways for Peptide Therapeutics: A Systematic Evaluation of USFDA and CDSCO Frameworks

Praveen R. B.*, Dr. C. Vijaya Raghavan

Chemists College of Pharmaceutical Sciences and Research, Ernakulam, Kerala, India.

ARTICLE INFO

Published: 07 Aug 2026
Keywords:
Peptide therapeutics, regulatory science, CDSCO, USFDA, approval pathways, Quality by Design, pharmacovigilance, insulin, regulatory harmonization, CMC requirements
DOI:
10.5281/zenodo.21838024

ABSTRACT

Background: Peptide therapeutics occupy a distinctive regulatory position between small-molecule drugs and biologics, creating unique challenges for global development. While the United States Food and Drug Administration (USFDA) and India's Central Drugs Standard Control Organization (CDSCO) both regulate these modalities, substantial heterogeneity persists in classification logic, Chemistry Manufacturing and Controls (CMC) expectations, clinical trial requirements, and post-approval lifecycle management. Objective: This study systematically compares regulatory frameworks governing peptide therapeutics between USFDA and CDSCO to identify convergence opportunities, regulatory gaps, and strategic considerations for multinational pharmaceutical development. Methods: A comparative analytical study was conducted via systematic literature review of regulatory documents and scientific literature spanning 2015–2025. A four-category comparative framework was developed encompassing regulatory parameters, technical and quality requirements, approval pathway analysis, and post-approval lifecycle management. A case study of insulin validated the framework. Results: USFDA operates under a highly centralized, scientifically rigorous system with advanced digital infrastructure, defined approval timelines under PDUFA, and extensive integration of Quality by Design (QbD) and Quality Risk Management (QRM). CDSCO provides a flexible, cost-effective framework with evolving international alignment, but demonstrates implementation variability, limited standardization in peptide classification, and lower adoption of advanced quality systems. The insulin case study confirmed divergence in regulatory classification, timeline predictability, and lifecycle control. Both authorities mandate preclinical evaluation and phased clinical development, yet differ substantially in technical documentation depth, transparency, and global harmonization leadership.

***Corresponding Author:** Praveen R. B.
Address: *Department of Pharmaceutical Regulatory Affairs, Chemists College of Pharmaceutical Sciences and Research, Ernakulam, Kerala, India.*
Email ✉: praveenbalakrishnan.rb@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Conclusions: Both authorities aim to ensure peptide therapeutic safety, efficacy, and quality, but USFDA represents a more mature, globally harmonized model. CDSCO requires further strengthening in standardization, digital infrastructure, and advanced quality integration to achieve comparable global acceptance

INTRODUCTION

Peptide therapeutics have emerged as one of the most promising classes of pharmaceutical agents, driven by advances in solid-phase peptide synthesis, recombinant DNA technology, and innovative drug delivery platforms (1). These pharmacologically active compounds, typically composed of 2–50 amino acid residues, occupy a distinctive regulatory position bridging conventional small-molecule drugs and complex biologics (2). This hybrid nature endows peptides with exceptional target specificity and favorable safety profiles, while simultaneously creating substantial regulatory complexity regarding classification, manufacturing control, and approval pathway determination (3). The therapeutic significance of peptide drugs has expanded across diabetes mellitus, oncology, cardiovascular disorders, and metabolic syndrome (4). Peptide hormone analogues such as insulin and glucagon-like peptide-1 receptor agonists have transformed long-term disease control, while peptide-based oncology agents enable receptor-specific targeting with minimized systemic toxicity (5). The global peptide therapeutics market continues to grow, supported by increasing regulatory approvals and expanding clinical pipelines (6). Despite their clinical promise, peptide therapeutics present unique regulatory challenges arising from susceptibility to enzymatic degradation, temperature sensitivity, potential aggregation, and structural heterogeneity that complicates analytical characterization (7). Unlike small-molecule drugs, peptides require advanced analytical techniques including mass spectrometry and circular dichroism to confirm primary sequence and higher-order structure (8). Conversely, although peptides share attributes with biologics, many lack post-translational modifications and complex folding patterns, creating ambiguity regarding regulatory classification as chemical drugs or biological products (9).

In the United States, the Food and Drug Administration regulates peptide therapeutics through a bifurcated system: chemically synthesized peptides under 40 amino acids generally follow New Drug Application pathways, while recombinant or complex peptides require Biologics License Applications (10). In India, the Central Drugs Standard Control Organization regulates peptides under the Drugs and Cosmetics Act, 1940, and New Drugs and Clinical Trials Rules, 2019 (8). However, CDSCO frequently applies biologic-like scrutiny based on manufacturing complexity regardless of peptide size, creating regulatory divergence from USFDA logic (11). These differences significantly influence development timelines, approval costs, and global commercialization strategies (12). The absence of harmonized classification criteria presents substantial challenges for multinational development, potentially resulting in study duplication and delayed patient access (13).

The present study systematically compares regulatory requirements and approval pathways for peptide therapeutics between USFDA and CDSCO, analyzing framework structure, technical expectations, approval mechanics, and post-approval lifecycle management to identify critical gaps and strategic recommendations for advancing global peptide therapeutic development.

MATERIALS AND METHODS

Study Design and Scope

This research was designed as a comparative, descriptive, and analytical study aimed at

evaluating regulatory requirements and approval pathways for peptide therapeutics under two major regulatory jurisdictions: the United States Food and Drug Administration and India's Central Drugs Standard Control Organization. The study focused specifically on understanding similarities, differences, strengths, and limitations of these regulatory systems as they apply to peptide-based pharmaceutical products, which represent an emerging therapeutic class requiring specialized regulatory consideration due to their intermediate molecular complexity and hybrid chemical-biological nature. The research scope encompassed the entire pharmaceutical product lifecycle from preclinical development through marketing authorization and post-approval surveillance. Regulatory pathways analyzed included the Investigational New Drug application, New Drug Application, and Biologics License Application under USFDA, and corresponding Indian pathways involving Clinical Trial Application and New Drug Approval procedures. The study was non-experimental in nature and relied extensively on secondary data obtained from regulatory documents, scientific literature, and official databases.

Literature Search and Data Collection Strategy

A comprehensive and systematic literature review was conducted to gather relevant information regarding peptide therapeutics and their regulatory approval processes across both jurisdictions. The data collection process was designed to ensure inclusion of authentic, current, and high-quality sources spanning the period 2015 to 2025. Primary data sources included official regulatory guidelines, policy documents, and notifications issued by recognized authorities(14). These comprised official publications and guidance documents from USFDA and CDSCO, international regulatory guidelines issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), including ICH Q7 (Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients), ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), ICH Q10 (Pharmaceutical Quality System), and ICH Q11 (Development and Manufacture of Drug Substances), as well as World Health Organization Technical Report Series documents (15). These primary sources provided the most reliable and legally binding information regarding regulatory expectations for peptide drugs, including quality, safety, and efficacy requirements.

Secondary sources were employed to supplement and interpret regulatory information, including peer-reviewed research articles and review papers from scientific journals related to pharmaceutical sciences and regulatory affairs, books and academic publications, regulatory intelligence reports and white papers, and online databases including PubMed, Scopus, ScienceDirect, and Google Scholar. The inclusion of secondary sources facilitated understanding of practical challenges, industry perspectives, and evolving regulatory trends in peptide therapeutics. To maintain quality and relevance, specific inclusion and exclusion criteria were applied. Inclusion criteria comprised publications between 2015 and 2025, documents specifically related to peptide therapeutics, regulatory guidelines from recognized authorities, and articles discussing approval pathways, clinical trials, and manufacturing requirements. Exclusion criteria eliminated outdated or superseded guidelines, non-peer-reviewed or unreliable sources, and studies unrelated to regulatory frameworks.

Stepwise Methodology

A systematic stepwise approach was followed to ensure structured data collection and analysis. The first step involved identification of relevant data

sources, wherein databases and regulatory platforms were identified for comprehensive coverage of both regulatory and scientific aspects. The second step employed a well-defined keyword strategy using terms including peptide therapeutics, regulatory approval pathways, USFDA approval process, CDSCO drug approval, IND, NDA, BLA, clinical trial approval India, biologics and peptide drugs, and regulatory harmonization, with Boolean operators employed to refine search results and improve relevance(16). The third step comprised screening and selection of literature based on relevance, authenticity, and applicability to the research objectives. Abstracts and summaries were initially reviewed, followed by full-text analysis of selected documents, with only sources providing substantial and reliable information retained for the study. The fourth step involved systematic data extraction of relevant information including regulatory framework and legal basis, approval pathways, clinical trial requirements and phases, manufacturing and quality control requirements, documentation and submission format, regulatory timelines and review procedures, and post-approval obligations and pharmacovigilance requirements. The fifth step cross-verified extracted data using multiple sources to ensure accuracy and reliability, with official regulatory portals and updated guidelines referred to confirm validity. The sixth step categorized validated data into specific segments such as regulatory, technical, and procedural parameters to enable systematic comparison between USFDA and CDSCO(17).

Development of the Comparative Framework

A comprehensive and structured comparative framework was developed to systematically evaluate regulatory requirements and approval pathways for peptide therapeutics in the United States and India. The framework was designed to enable clear comparison between regulatory systems and was divided into four major categories representing critical components of the regulatory system. The regulatory and administrative framework category focused on structural, legal, and administrative aspects governing peptide therapeutic approval. The technical and quality requirements category evaluated scientific and technical requirements associated with peptide therapeutic development and approval. The approval pathway analysis category focused on the stepwise regulatory approval process. The post-approval and lifecycle management category included regulatory requirements following drug approval, focusing on pharmacovigilance, post-marketing surveillance, and lifecycle management(18).

Case Study Validation

To validate the developed comparative framework, a detailed case study approach was adopted using a representative peptide therapeutic. Insulin was selected as the model drug based on several considerations: it is a globally approved peptide therapeutic with well-established regulatory pathways in both the United States and India; extensive data is available regarding its manufacturing, quality control, and clinical studies; it is included in the World Health Organization Essential Medicines List; and it represents a benchmark molecule for peptide drug regulation due to its widespread therapeutic importance and regulatory history. (19,20)

RESULTS

Regulatory and Administrative Framework

The regulatory and administrative framework constitutes the structural backbone of drug approval processes and plays a crucial role in determining efficiency, transparency, and predictability of regulatory systems. For peptide

therapeutics, this framework becomes particularly significant due to the complex nature of these molecules, which require specialized regulatory oversight, stringent documentation, and well-defined approval pathways.

Table 1 presents the comparative evaluation of regulatory and administrative parameters between CDSCO and USFDA. The United States Food and Drug Administration operates under a highly centralized and well-defined regulatory system ensuring uniformity, transparency, and consistency in decision-making. The organizational structure involves specialized centers including the Center for Drug Evaluation and Research, which regulates chemically synthesized peptide drugs categorized as pharmaceutical products, and the Center for Biologics Evaluation and Research, which oversees recombinant or biotechnology-derived peptide therapeutics classified as biologics (21). This centralized approach ensures consistent regulatory decisions, uniform implementation of guidelines, and efficient coordination between functional units, with dedicated review teams for biologics and complex therapeutics enhancing the quality and depth of scientific evaluation.

Table 1. Comparative Outcome: Regulatory and Administrative Framework for Peptide Therapeutics.(22,23)

Parameter	CDSCO (India)	USFDA (United States)
Governing Authority	CDSCO under MoHFW; supported by DCGI, SECs, zonal/state authorities	USFDA through CDER/CBER; highly centralize
Regulatory Structure	Multi-tiered; central and state authorities; variability in implementation	Highly centralized; uniform implementation and consistent decision-making
Legal Framework	Drugs & Cosmetics Act, 1940; no dedicated peptide-specific or biologics law	FD&C Act; PHS Act; well-defined biologics provisions
Classification of Peptide Therapeutics	Under new drugs or biologics depending on complexity; lacks clear categorization	Clearly classified; <40 amino acids chemically synthesized = small molecule; recombinant = biologic (BLA)
Submission Format	CTD and eCTD accepted; transition phase with hybrid submissions common	Mandatory eCTD submission; globally harmonized format
Electronic Submission System	SUGAM portal; partial digitalization	Fully digital ESG; advanced automation and validation tools
Digital Infrastructure Maturity	Developing; some processes still manual or semi-digital	Highly advanced; complete digital lifecycle management
Approval Timelines	Variable; depends on case complexity and administrative processes	Defined timelines under PDUFA; predictable and structured
Transparency and Communication	Moderate; limited public access to review status and approval data	High transparency; public databases, review summaries, and regulatory decisions available
Fee Structure	Relatively low fees; cost-effective for industry	High user fees (PDUFA); supports regulatory efficiency and staffing
Administrative Efficiency	Moderate; influenced by multiple regulatory layers	High efficiency due to centralized and automated systems
Regulatory Guidance Availability	Limited and dispersed guidance documents	Extensive and regularly updated guidance documents

Review Coordination	Multiple committees involved; may lead to delays	Streamlined review through specialized divisions
International Harmonization	Partial alignment with ICH guidelines	Strong alignment; actively contributes to ICH development
Ease of Filing	Moderate; requires interpretation of multiple documents	High; clearly defined submission pathways
Regulatory Predictability	Moderate; variability exists	High; predictable outcomes based on structured framework
Communication Mechanism	Email, portal, and manual correspondence	Structured communication via ESG and official regulatory letters
Record Management	Semi-digital; limited traceability	Fully digital with audit trails and version control

In contrast, the Central Drugs Standard Control Organization operates under a multi-tiered framework involving central authorities, state regulatory bodies, and expert committees. While this structure allows for distributed regulatory control, it can introduce variability in decision-making, procedural delays, and inconsistencies in regulatory interpretation (24). The involvement of multiple administrative levels may affect uniformity of regulatory outcomes, particularly for complex submissions requiring specialized scientific evaluation.

The legal framework governing drug approval represents another critical area of divergence. The USFDA regulatory system is supported by well-defined legal provisions under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, which provide explicit guidance for biologics regulation including peptide therapeutics and establish clear pathways such as the Biologics License Application. This legal clarity enhances regulatory predictability and ensures applicants have a well-defined understanding of submission requirements. CDSCO relies primarily on the Drugs and Cosmetics Act, 1940, which was originally designed for conventional pharmaceutical products and does not provide specific provisions for peptide therapeutics or advanced biologics, resulting in classification ambiguity and variable interpretation (25).

Digital infrastructure represents a major differentiating factor between the two regulatory systems. USFDA has achieved high digital maturity through implementation of the Electronic Submission Gateway and mandatory electronic Common Technical Document submissions, enabling efficient document submission, automated validation, real-time tracking, and structured communication between applicants and regulators. CDSCO has made significant progress through introduction of the SUGAM portal, representing an important step toward digital transformation; however, the system currently operates as a semi-digital platform with certain processes still relying on manual intervention and offline communication, potentially resulting in delays and reduced transparency (26).

Approval timelines reflect further differences in regulatory efficiency. USFDA operates under well-defined timelines established through the Prescription Drug User Fee Act, ensuring timely review of applications and predictable approval processes supported by adequate staffing and structured review cycles. CDSCO approval timelines are more variable and may depend on factors such as application complexity, workload, and administrative procedures, introducing uncertainty for applicants and affecting strategic planning for product development and market entry (27).

Transparency and accessibility of regulatory information also distinguish the two systems. USFDA maintains high transparency by providing public access to regulatory decisions, approval reports, clinical data summaries, and safety information through integrated databases including Drugs@FDA, ClinicalTrials.gov, and the FDA Adverse Event Reporting System. This openness supports academic research, enhances industry compliance, and builds public trust. CDSCO, while improving, currently offers limited public access to detailed regulatory data, with information such as approval timelines, review status, and decision-making processes not always readily available (28).

Technical and Quality Requirements

Technical and quality requirements represent the scientific foundation of regulatory evaluation for peptide therapeutics. Unlike conventional small-molecule drugs, peptide therapeutics exhibit higher molecular complexity, structural sensitivity, and susceptibility to degradation, necessitating stringent requirements for manufacturing processes, analytical characterization, impurity profiling, and stability evaluation.

Table 2 presents the comparative evaluation of technical and quality parameters. Good Manufacturing Practice compliance demonstrates substantial differences between the two systems. USFDA enforces strict compliance with current Good Manufacturing Practice regulations under 21 CFR Parts 210 and 211, supported by routine and risk-based inspections that focus on ensuring data integrity, process control, and overall manufacturing quality. CDSCO enforces GMP requirements under Schedule M, which has been progressively updated to align with international standards such as ICH Q7; however, implementation and enforcement may vary across manufacturing facilities and regions, potentially affecting consistency in quality standards (29).

Table 2. Comparative Outcome: Technical and Quality Requirements for Peptide Therapeutics(30)

Parameter	CDSCO (India)	USFDA (United States)
GMP Compliance	Based on Schedule M; gradually aligning with ICH Q7; enforcement varies across facilities	Strict adherence to ICH Q7 and cGMP (21 CFR Parts 210, 211); highly enforced through routine inspection
Peptide Characterization	Requires basic structural and physicochemical characterization; reliance on pharmacopoeial standards	Requires comprehensive characterization including primary, secondary, tertiary structure, and conformational analysis
Manufacturing Process Description	Requires process flow, equipment details, and critical steps; limited emphasis on design space	Highly detailed process description including critical process parameters, control strategy, and design space
Process Validation	Validation required; retrospective validation sometimes accepted	Lifecycle-based validation mandatory (process design, qualification, continued verification)
Impurity Profiling	Primarily based on pharmacopoeial limits; limited impurity fate studies	Extensive impurity profiling with ICH Q3A/B and ICH M7 compliance; includes toxicological qualification
Analytical Method Validation	Accepts ICH Q2 guidelines; may accept pharmacopoeial methods without full validation	Full validation required including accuracy, precision, specificity, robustness, and linearity
Stability Studies	Based on ICH Q1A; focus on Zone IVb (30°C/75% RH) conditions	Comprehensive stability data across multiple conditions; multi-batch studies required

Specification Standards	Accepts IP, BP, USP standards; flexibility allowed	Requires scientifically justified specifications aligned with USP and ICH
Raw Material Control	Relies on supplier certificates and basic testing	Requires detailed characterization and risk assessment of raw materials and intermediates
Quality Risk Management (QRM)	Limited implementation; evolving in industry	Mandatory as per ICH Q9; extensive use of risk assessment tools
Quality by Design (QbD)	Not mandatory; limited adoption	Strongly encouraged; often expected in submissions
Batch Consistency	Basic batch data required	Extensive multi-batch data required to demonstrate consistency
Degradation Studies	Limited forced degradation studies	Comprehensive forced degradation and pathway analysis required
Control Strategy	Basic control strategy	Advanced, science-based control strategy
Documentation Depth	Moderate	Highly detailed and scientifically rigorous

Impurity profiling is particularly critical for peptide therapeutics due to susceptibility to degradation and formation of related substances. USFDA requires comprehensive impurity profiling in accordance with ICH Q3A, ICH Q3B, and ICH M7 guidelines, including identification, qualification, and toxicological assessment of impurities along with detailed studies on impurity formation pathways and purge mechanisms. CDSCO generally relies on pharmacopoeial limits for impurity control, ensuring compliance with established standards but potentially lacking complete understanding of impurity behavior and toxicological significance (31).

Analytical method validation expectations differ substantially. USFDA requires complete validation data for all analytical methods, including accuracy, precision, specificity, linearity, and robustness parameters, ensuring reliability and reproducibility of analytical results. CDSCO accepts ICH Q2 guidelines but may allow use of pharmacopoeial methods without full validation datasets, reducing documentation burden but potentially affecting depth of analytical evaluation. Stability study requirements reveal further divergence. USFDA requires stability data across multiple climatic zones, including long-term and accelerated studies on multiple batches, supporting global distribution and ensuring product stability under diverse environmental conditions. CDSCO focuses primarily on Zone IVb conditions relevant to the Indian climate, ensuring local applicability but potentially limiting global generalization of stability data (32).

The integration of advanced quality systems represents perhaps the most significant technical divergence. USFDA strongly emphasizes Quality by Design and Quality Risk Management, requiring applicants to demonstrate scientific understanding of product and process variability with risk assessment tools such as Failure Mode and Effects Analysis commonly used to identify and mitigate potential risks. CDSCO, while recognizing these concepts, has not yet made them mandatory, and their implementation remains limited in practice, resulting in a more compliance-oriented rather than science-driven regulatory approach (33).

Approval Pathway Analysis

The approval pathway defines the systematic progression of drug candidates from preclinical development to final market authorization. For peptide therapeutics, this process requires careful evaluation due to structural complexity, biological activity, and potential immunogenicity.

Table 3 presents the comparative evaluation of approval pathway parameters. Preclinical development stages demonstrate significant differences in regulatory expectations. USFDA imposes highly structured preclinical study requirements with extensive expectations regarding study design, documentation, and compliance with Good Laboratory Practices, ensuring a robust scientific foundation before human trials (34). This includes detailed toxicological evaluation, pharmacokinetic and pharmacodynamic characterization, genotoxicity assessment, and safety pharmacology studies. CDSCO mandates essential preclinical studies including acute, sub-acute, and chronic toxicity evaluations along with pharmacokinetic and pharmacodynamic assessments conducted per Schedule Y guidelines; however, the depth of study design and reporting may vary depending on drug nature and prior available data (35).

Table 3. Comparative Outcome: Approval Pathway Analysis for Peptide Therapeutics

Parameter	CDSCO (India)	USFDA (United States)
Preclinical Study Requirements	Mandatory per Schedule Y; depth may vary depending on drug nature and prior data	Extensive, highly structured; GLP mandatory; includes toxicological, PK/PD, genotoxicity, and safety pharmacology
Type of Initial Regulatory Submission	Clinical Trial Application (CTA) to CDSCO with preclinical data, protocol details, and investigator information	Investigational New Drug (IND) application with detailed preclinical data, manufacturing processes, and clinical trial protocols
Clinical Trial Authorization Process	Approval by CDSCO in conjunction with Ethics Committees; SEC review for certain categories; timelines vary	IND clearance by USFDA and IRB approval; highly structured with defined timelines and regulatory checkpoints
Clinical Trial Phases	Phase I, II, and III required; flexibility exists for waivers or bridging studies with sufficient international data	Strict enforcement of Phase I (safety), Phase II (efficacy and dose optimization), and Phase III (large-scale confirmation)
Clinical Trial Monitoring and Oversight	Monitored by CDSCO and Ethics Committees; periodic inspections; intensity may vary across sites	Rigorously monitored by USFDA, IRBs, and Data Safety Monitoring Boards; continuous oversight ensures GCP compliance
Marketing Authorization Submission	New Drug Application or biologics-related dossier; CTD format; may involve flexibility depending on prior approval	NDA (505(b)(1)/(b)(2)) or BLA depending on classification; highly detailed eCTD submission with extensive scientific data
Review Process and Evaluation	Multiple regulatory bodies including CDSCO officials and SEC; iterative queries and discussions	Centralized multidisciplinary teams; consistent and scientifically rigorous evaluation
Approval Timelines	Variable; depend on application complexity, administrative processes, and regulatory workload; predictability relatively lower	Well-defined under PDUFA; predictable review cycles; standard and priority review timelines clearly specified
Accelerated Approval Mechanisms	No well-defined structured pathways; case-based flexibility for urgent medical needs	Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval programs
Risk-Benefit Assessment Approach	Performed based on available data and expert committee recommendations; relatively flexible approach	Highly structured quantitative framework incorporating statistical analysis, safety data, and therapeutic benefit evaluation

Post-Submission Communication	Email, meetings, and portal interactions; may lack standardized timelines	Structured communication through Complete Response Letters ensuring clarity in addressing deficiencies
Transparency of Approval Decisions	Limited public disclosure of detailed review reports and approval rationale	High transparency with publicly available approval summaries, clinical reviews, and decision documents
Global Regulatory Acceptance	Primarily recognized in domestic and semi-regulated markets	Globally recognized; often serves as benchmark for regulatory acceptance worldwide

Clinical trial initiation procedures highlight structural differences between the two systems. The Investigational New Drug application under USFDA represents a highly organized and scientifically rigorous process wherein detailed evaluation of preclinical safety data, manufacturing information, analytical characterization, clinical trial protocols, and investigator credentials is conducted before granting permission for clinical studies. Clinical trials may begin if no regulatory objections are raised within thirty days, providing predictable timelines. The Clinical Trial Application process under CDSCO involves multiple administrative and ethical layers including CDSCO review, Ethics Committee approval, and potential Subject Expert Committee evaluation depending on drug category, which may introduce variability in approval timelines (36).

Clinical trial conduct and oversight are more stringent under USFDA, with continuous monitoring by multiple regulatory bodies including Institutional Review Boards and Data Safety Monitoring Boards, and strict adherence to Good Clinical Practice guidelines throughout all phases. CDSCO also ensures ethical compliance through clinical trial monitoring by regulatory authorities and Ethics Committees; however, the intensity and consistency of monitoring may vary across trial sites. Marketing authorization pathways reflect the highest level of regulatory divergence. USFDA's New Drug Application and Biologics License Application pathways are supported by extensive scientific evaluation and multidisciplinary review, ensuring high confidence in safety and efficacy of approved products (37). The NDA for chemically synthesized peptides contains comprehensive documentation related to quality and manufacturing data, non-clinical studies, clinical trial results, risk-benefit evaluation, and labeling information, while the BLA for recombinant peptides emphasizes biological activity, manufacturing process validation, and product consistency. CDSCO follows a similar structural approach for New Drug Approval but with comparatively less standardization in review procedures, and the approval pathway may involve flexibility depending on prior approvals for well-established drugs. Approval timelines represent a major advantage of the USFDA system. Defined timelines under the Prescription Drug User Fee Act provide predictability and facilitate strategic planning for pharmaceutical companies, with standard and priority review timelines clearly specified. CDSCO timelines, while sometimes faster due to flexibility, lack consistency and predictability, which may affect development planning and resource allocation (38).

A notable strength of the USFDA system is the presence of structured accelerated approval pathways. Fast Track Designation, Breakthrough Therapy Designation, Accelerated Approval, and Priority Review programs enable faster access to life-saving therapies addressing serious or life-threatening diseases without compromising regulatory standards for safety and effectiveness. CDSCO currently lacks such well-defined

structured accelerated pathways, although case-based flexibility is occasionally applied in specific situations, potentially limiting rapid introduction of innovative therapies in the Indian market. Risk-benefit assessment is more scientifically rigorous and quantitatively driven in the USFDA framework, incorporating advanced statistical analysis, comprehensive data evaluation, and structured benefit-risk determination. CDSCO relies more on expert committee recommendations with a relatively flexible approach, providing adaptability but potentially reducing standardization in decision-making (39).

Post-Approval and Lifecycle Management

Post-approval and lifecycle management ensure pharmaceutical products continue meeting safety, efficacy, and quality standards after market authorization. For peptide therapeutics, this stage is particularly important due to susceptibility to degradation, potential immunogenicity, and sensitivity to manufacturing variations.

Table 4 presents the comparative evaluation of post-approval and lifecycle management parameters. Pharmacovigilance systems represent the foundation of post-marketing safety monitoring. USFDA operates the FDA Adverse Event Reporting System, a highly advanced and globally integrated pharmacovigilance database that enables real-time monitoring of adverse events and supports advanced signal detection using statistical and computational tools. CDSCO operates through the Pharmacovigilance Programme of India, which has significantly improved adverse drug reaction reporting since establishment but continues to face challenges related to underreporting, limited awareness among healthcare professionals, and variability in data collection infrastructure (40).

Table 4. Comparative Outcome: Post-Approval and Lifecycle Management of Peptide Therapeutics(41,42)

Parameter	CDSCO (India)	USFDA (United States)
Pharmacovigilance System	Pharmacovigilance Programme of India (PvPI); collects ADR data from hospitals and healthcare centers; reporting compliance and data integration still evolvin	FDA Adverse Event Reporting System (FAERS); highly structured comprehensive database with advanced signal detection capabilities
Adverse Event Reporting	Reporting encouraged but underreporting remains a challenge due to lack of awareness and limited infrastructure in certain region	Mandatory reporting requirements for manufacturers and healthcare professionals; high data reliability and robust safety monitoring
Post-Marketing Surveillance	Conducted through periodic safety reports and observational studies; implementation may vary	Highly structured including Phase IV studies, risk evaluation programs, and continuous safety monitoring
Risk Management Plans (RMP)	Not consistently mandatory; implemented in specific cases depending on product risk profile	Mandatory Risk Evaluation and Mitigation Strategies (REMS) for high-risk drugs ensuring controlled distribution and safe use
Lifecycle Management Approach	Basic lifecycle management with limited structured framework; changes handled on a case-by-case basis	Comprehensive lifecycle management covering product development, approval, and post-marketing phases with continuous monitorin

Post-Approval Changes (PAC)	Manufacturing modifications or formulation updates allowed; regulatory categorization (minor/major) may not always be clearly defined	Strict classification of changes (minor, moderate, major) with clearly defined regulatory pathways and prior approval requirements
Stability Monitoring Post-Approval	Stability studies conducted but long-term monitoring systems may not be consistently enforced	Continuous stability monitoring required with commitment batches and annual reporting to ensure product quality throughout shelf life
Periodic Safety Update Reports (PSUR)	Required submission of PSURs; frequency and enforcement may vary	Periodic Benefit-Risk Evaluation Reports (PBRER) required with strict timelines and detailed safety analysis
Inspection and Compliance Monitoring	Periodic inspections conducted; frequency may vary depending on resource availability	Regular and risk-based inspections conducted with strict enforcement of compliance and data integrity standards
Product Recall System	Recall procedures exist but may vary in execution efficiency and response time	Highly efficient and structured recall system with rapid response mechanisms and public notification protocols
Transparency of Safety Data	Limited public access to detailed safety data and regulatory decisions	High transparency with publicly accessible safety alerts, adverse event data, and regulatory actions
Traceability and Documentation	Semi-digital documentation systems with limited integration	Fully digital documentation with complete traceability, audit trails, and real-time monitoring systems
Regulatory Communication	Communication through official letters, emails, and portal systems; may lack structured timelines	Structured and time-bound communication through formal regulatory channels ensuring clarity and efficiency
Global Integration	Limited integration with global pharmacovigilance system	Strong integration with international safety monitoring systems and regulatory collaborations

Adverse event reporting practices further highlight differences in regulatory enforcement. USFDA mandates strict reporting requirements for pharmaceutical companies and healthcare professionals, ensuring comprehensive and reliable safety data. CDSCO encourages reporting, but compliance may vary across regions and institutions, potentially impacting completeness of safety data and timeliness of signal detection. Post-marketing surveillance is more structured under USFDA through requirements for Phase IV clinical trials, continuous safety monitoring, risk evaluation programs, and periodic benefit-risk reassessment. CDSCO also requires post-marketing surveillance; however, implementation and enforcement may not be as consistent across all approved products. Risk management represents a key component of lifecycle control, particularly for peptide therapeutics with complex safety profiles. USFDA requires Risk Evaluation and Mitigation Strategies for certain drugs, which include measures such as restricted distribution, patient monitoring, and healthcare provider training to ensure safe use. CDSCO does not have a uniformly implemented risk management framework, although such strategies may be applied in specific cases depending on product risk profile. Lifecycle management under USFDA

follows a highly structured approach integrating product development, regulatory approval, and post-marketing monitoring into a continuous process, ensuring changes in manufacturing, formulation, or quality attributes are carefully evaluated and controlled through well-defined regulatory pathways. CDSCO manages lifecycle changes on a case-by-case basis, which may lack equivalent standardization and could introduce variability in regulatory decisions (43).

+***Case Study: Insulin***

The case study of insulin provides practical validation of the comparative framework and demonstrates real-world application of regulatory differences between USFDA and CDSCO. Insulin, a peptide hormone consisting of amino acid chains regulating blood glucose levels, is primarily used in diabetes mellitus management and represents one of the earliest and most successful therapeutic applications of peptide hormones.

Table 5 presents the comparative evaluation of insulin regulation. Regulatory classification constitutes a fundamental difference in insulin oversight. Under USFDA, insulin is clearly regulated as a biologic under the Biologics License Application pathway, particularly following its transition from New Drug Application to BLA classification, ensuring strict regulatory control appropriate for its biological complexity. Under CDSCO, insulin is classified as a biologic or new drug depending on formulation and manufacturing process, with the classification framework less explicitly defined for peptides, potentially leading to variable regulatory interpretation(44).

Table 5. Comparative Evaluation of Insulin as a Peptide Therapeutic

Parameter	USFDA (United States)	CDSCO (India)
Regulatory Classification	Biologic (regulated under BLA pathway, particularly after transition from NDA to BLA)	Biologic/New Drug (hybrid classification depending on formulation and manufacturing process)
Governing Regulatory Body	Center for Biologics Evaluation and Research (CBER) or CDER depending on classification	CDSCO under Ministry of Health, with involvement of Subject Expert Committees for evaluation
Approval Pathway	BLA (Biologics License Application) requiring extensive clinical, non-clinical, and manufacturing data	New Drug Approval via CDSCO; pathway may involve flexibility depending on prior approvals
Preclinical Requirements	Extensive preclinical evaluation required even for known molecules, including detailed toxicological and pharmacological studies	Basic preclinical studies required; reliance on known safety profile of insulin may reduce data requirements
Clinical Trial Requirements	Full clinical trial data required unless specific biosimilar pathways are followed; strict adherence to Phase I–III or biosimilar guidelines	Clinical trials required; waivers or bridging studies may be accepted for well-established drugs like insulin
Manufacturing Process Control	Strict cGMP and ICH Q7 compliance; detailed process control, validation, and monitoring required	Manufacturing must comply with GMP (Schedule M); process control requirements defined but may vary in implementation
Analytical Characterization	Comprehensive analytical characterization required including structural, functional, and stability analysis using advanced techniques	Basic analytical characterization required, including purity and potency testing

Impurity and Stability Control	Extensive impurity profiling and stability studies across multiple conditions with detailed degradation pathway analysis	Impurity limits based on pharmacopoeial standards; stability studies conducted under Zone IVb conditions
Regulatory Review Process	Centralized and highly structured review process with multidisciplinary evaluation teams	Multi-level review involving CDSCO and expert committees; timelines may vary
Approval Timelines	Defined timelines under PDUFA ensuring predictable approval cycles	Variable timelines depending on regulatory and administrative factors
Post-Approval Monitoring	Continuous monitoring through FAERS with advanced signal detection and safety evaluation	Pharmacovigilance through PvPI; monitoring systems functional but evolving
Lifecycle Management	Comprehensive lifecycle management with strict control over manufacturing changes and continuous monitoring	Post-approval changes handled on case-by-case basis; limited structured lifecycle framework
Global Acceptance	Globally recognized standard; facilitates international market access	Primarily accepted in domestic and semi-regulated markets12

Preclinical requirements for insulin demonstrate the higher scientific rigor of USFDA evaluation. Extensive preclinical evaluation is required even for well-established molecules, including detailed toxicological and pharmacological studies, to support the safety profile before human trials. CDSCO requires basic preclinical studies but may rely on the known safety profile of insulin and existing literature, potentially reducing data requirements for this established therapeutic. Clinical trial requirements also reveal divergence. USFDA requires full clinical trial data unless specific biosimilar pathways are followed, with strict adherence to Phase I through III studies or biosimilar guidelines ensuring comprehensive safety and efficacy evaluation. CDSCO requires clinical trials but may accept waivers or bridging studies for well-established drugs such as insulin, facilitating faster approval but potentially introducing variability in data robustness (45).

Manufacturing process control expectations differ substantially. USFDA enforces strict current Good Manufacturing Practice compliance with detailed process validation and monitoring requirements, ensuring every batch meets predefined quality standards. CDSCO requires Schedule M GMP compliance, but the level of enforcement and process understanding may vary across manufacturing facilities. Analytical characterization is more comprehensive under USFDA, with requirements for structural, functional, and stability analysis using advanced techniques to evaluate molecular integrity and potency. CDSCO generally requires basic purity and potency testing, which ensures essential quality parameters but may not capture all aspects of molecular complexity(46).

Stability requirements under USFDA mandate comprehensive studies across multiple conditions with detailed degradation pathway analysis to ensure product performance under global distribution scenarios. CDSCO focuses stability studies on Zone IVb conditions relevant to the Indian climate, ensuring local applicability but potentially limiting global generalization (2). Approval timelines for insulin are defined under USFDA through PDUFA, ensuring predictable review cycles. CDSCO timelines remain variable depending on regulatory and administrative factors. Post-approval monitoring systems demonstrate significant divergence. USFDA utilizes the FDA Adverse Event Reporting System with advanced signal detection and safety evaluation capabilities for continuous monitoring. CDSCO operates through the Pharmacovigilance Programme of India, which is functional but still

developing in terms of reporting efficiency and data integration(47).

DISCUSSION

This study reveals fundamental differences in regulatory philosophy, structural design, and operational efficiency between CDSCO and USFDA that significantly impact global peptide therapeutic development. The analysis across four critical domains regulatory framework, technical requirements, approval pathways, and post-approval management demonstrates that USFDA operates as a globally recognized benchmark with centralized control, well-defined legal provisions, and advanced digital infrastructure. CDSCO's multi-tiered structure introduces variability affecting predictability, with absence of dedicated peptide-specific legislation creating classification ambiguity that complicates sponsor navigation. The divergence in technical requirements is particularly significant given peptide structural complexity. USFDA's emphasis on Quality by Design, Quality Risk Management, and lifecycle-based process validation reflects a science-driven philosophy ensuring deep understanding of product quality. CDSCO's compliance-oriented approach, while functional for basic standards, may limit scientific depth and global acceptability for export products. The gap in impurity profiling where USFDA requires toxicological qualification per ICH M7 while CDSCO relies on pharmacopoeial limits exemplifies this divergence with practical safety implications. Defined timelines under PDUFA provide USFDA major advantages in predictability, facilitating strategic planning and investor confidence. CDSCO's variable timelines, while sometimes enabling faster approvals, introduce uncertainty affecting development planning and market access. Absence of structured accelerated pathways in India may disadvantage patients with serious conditions requiring innovative therapies.

USFDA's FAERS system represents pharmacovigilance gold standard with real-time monitoring and advanced signal detection. CDSCO's Pharmacovigilance Programme of India shows progress but faces challenges in reporting compliance and infrastructure limiting effectiveness. USFDA's active ICH leadership facilitates strong international alignment and global market access, while CDSCO requires more consistent guideline implementation. Sponsors should adopt USFDA-quality science early, implementing QbD principles and robust risk management to facilitate multi-regional submissions. The insulin case study validates that regulatory divergence has tangible implications for development, manufacturing investment, and market access strategies.

CONCLUSION

This comparative study demonstrates that while both the Central Drugs Standard Control Organization and the United States Food and Drug Administration share the fundamental objective of ensuring the safety, efficacy, and quality of peptide therapeutics, their regulatory approaches differ significantly in structure, scientific depth, and operational efficiency. The United States Food and Drug Administration represents a highly mature, structured, and globally harmonized regulatory model characterized by centralized authority, advanced digital infrastructure, rigorous science-based quality expectations, defined approval timelines, structured accelerated pathways, and comprehensive post-approval surveillance. The Central Drugs Standard Control Organization provides a functional, flexible, and cost-effective regulatory environment with adaptability to local healthcare needs and progressive alignment with international standards, yet requires further strengthening in regulatory standardization, digital transformation, and integration of advanced quality systems to

achieve comparable global acceptance. Key recommendations emerging from this analysis include the development of peptide-specific regulatory guidance to reduce classification ambiguity, enhancement of digital infrastructure through full electronic Common Technical Document implementation and integrated database development, mandatory integration of Quality by Design and Quality Risk Management principles for complex therapeutic products, establishment of structured accelerated approval pathways for unmet medical needs, strengthening of the Pharmacovigilance Programme of India through improved reporting infrastructure and global integration, and increased regulatory transparency via public access to approval data and regulatory decisions. Regulatory harmonization between these systems will be essential for supporting global development of peptide therapeutics and ensuring timely patient access to innovative therapies. The continued evolution of both frameworks toward convergence on scientific best practices, while respecting local healthcare contexts, represents the optimal path forward for this important therapeutic class.

AUTHOR CONTRIBUTIONS

Conceptualization: Praveen R.B.; Methodology: Praveen R.B., Dr. C. Vijaya Raghavan; Investigation: Praveen R.B.; Writing – Original Draft: Praveen R.B.; Writing – Review & Editing: Dr. C. Vijaya Raghavan; Supervision: Dr. C. Vijaya Raghavan.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING

This research received no external funding.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the guidance and support of the faculty and staff of Chemists College of Pharmaceutical Sciences and Research, Ernakulam, Kerala, India.

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HOW TO CITE: Praveen R. B., Dr. C. Vijaya Raghavan, Comparative Analysis of Regulatory Requirements and Approval Pathways for Peptide Therapeutics: A Systematic Evaluation of USFDA and CDSCO Frameworks, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 8, 1285-1303, https://doi.org/10.5281/zenodo.21838024